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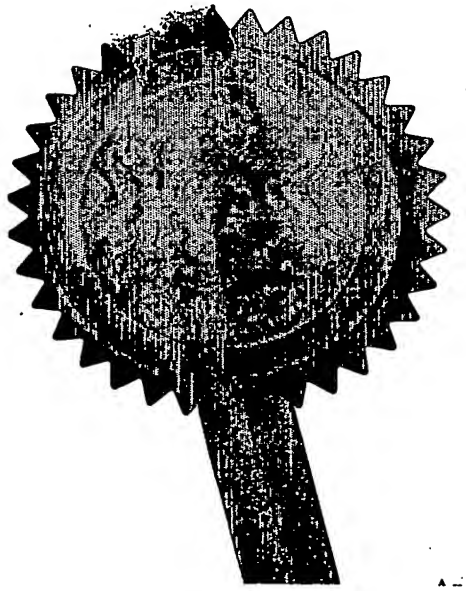

Signed P. Mahoney

Dated 28 August 2003

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1. Your reference — AST5 (P015)

2. Patent application number *(The Patent Office will fill in this part)* — 0218625.2

12AUG02 E740152-1 C81430 10 AUG 200
P01/7700 0.00-0218625.2

3. Full name, address and postcode of the or each applicant *(underline all surnames)*

Astex Technology Limited
250 Cambridge Science Park
Milton Road
Cambridge
CB4 0WE
United Kingdom

Patents ADP number *(if you know it)* — C81430 8118831700 1

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — PHARMACEUTICAL COMPOUNDS

Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

M. R. Hutchins & Co
33 Connaught Way
Tunbridge Wells
TN4 9QP
844 329 3001

Patents ADP number *(if you know it)*

5. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*

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Number of earlier application	Date of filing *(day/month/year)*

7. Is a statement of inventorship and or right to grant of a patent required in support of this request?
(Answer 'Yes' if:
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body;
See note (d)

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Description	53
Claim(s)	11
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Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature [signature] Date 8 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Michael R. Hutchins
01892 539659

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PHARMACEUTICAL COMPOUNDS

This invention relates to 3-substituted indazole compounds that inhibit or modulate the activity of cyclin dependent kinases (CDK), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by cyclin dependent kinases, and to novel compounds having cyclin dependent kinase inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II,* Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.,* 9:576-596 (1995); Knighton, *et al.*, *Science,* 253:407-414 (1991); Hiles, *et al.*, *Cell,* 70:419-429 (1992); Kunz, *et al.*, *Cell,* 73:585-596 (1993); Garcia-Bustos, *et al.*, *EMBO J.,* 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These

phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

The process of eukaryotic cell division may be broadly divided into a series of sequential phases termed G1, S, G2 and M. Correct progression through the various phases of the cell cycle has been shown to be critically dependent upon the spatial and temporal regulation of a family of proteins known as cyclin dependent kinases (cdks) and a diverse set of their cognate protein partners termed cyclins. Cdks are cdc2 (also known as cdk1) homologous serine-threonine kinase proteins that are able to utilise ATP as a substrate in the phosphorylation of diverse polypeptides in a sequence dependent context. Cyclins are a family of proteins characterised by a homology region, containing approximately 100 amino acids, termed the "cyclin box" which is used in binding to, and defining selectivity for, specific cdk partner proteins.

Modulation of the expression levels, degradation rates, and activation levels of various cdks and cyclins throughout the cell cycle leads to the cyclical formation of a series of cdk/cyclin complexes, in which the cdks are enzymatically active. The formation of these complexes controls passage through discrete cell cycle checkpoints and thereby enables the process of cell division to continue. Failure to satisfy the pre-requisite biochemical criteria at a given cell cycle checkpoint, *i.e.*

failure to form a required cdk/cyclin complex, can lead to cell cycle arrest and/or cellular apoptosis. Aberrant cellular proliferation, as manifested in cancer, can often be attributed to loss of correct cell cycle control. Inhibition of cdk enzymatic activity therefore provides a means by which abnormally dividing cells can have their division arrested and/or be killed. The diversity of cdks, and cdk complexes, and their critical roles in mediating the cell cycle, provides a broad spectrum of potential therapeutic targets selected on the basis of a defined biochemical rationale.

Progression from the G1 phase to the S phase of the cell cycle is primarily regulated by cdk2, cdk3, cdk4 and cdk6 via association with members of the D and E type cyclins. The D-type cyclins appear instrumental in enabling passage beyond the G1 restriction point, where as the cdk2/cyclin E complex is key to the transition from the G1 to S phase. Subsequent progression through S phase and entry into G2 is thought to require the cdk2/cyclin A complex. Both mitosis, and the G2 to M phase transition which triggers it, are regulated by complexes of cdk1 and the A and B type cyclins.

During G1 phase Retinoblastoma protein (Rb), and related pocket proteins such as p130, are substrates for cdk(2, 4, & 6)/cyclin complexes. Progression through G1 is in part facilitated by hyperphosphorylation, and thus inactivation, of Rb and p130 by the cdk(4/6)/cyclin-D complexes. Hyperphosphorylation of Rb and p130 causes the release of transcription factors, such as E2F, and thus the expression of genes necessary for progression through G1 and for entry into S-phase, such as the gene for cyclin E. Expression of cyclin E facilitates formation of the cdk2/cyclin E complex which amplifies, or maintains, E2F levels via further phosphorylation of Rb. The cdk2/cyclin E complex also phosphorylates other proteins necessary for DNA replication, such as NPAT, which has been implicated in histone biosynthesis. G1 progression and the G1/S transition are also regulated via the mitogen stimulated Myc pathway, which feeds into the cdk2/cyclin E pathway. Cdk2 is also connected to the p53 mediated DNA damage response pathway via p53 regulation of p21 levels. p21 is a protein inhibitor of cdk2/cyclin E and is thus capable of

blocking, or delaying, the G1/S transition. The cdk2/cyclin E complex may thus represent a point at which biochemical stimuli from the Rb, Myc and p53 pathways are to some degree integrated. Cdk2 and/or the cdk2/cyclin E complex therefore represent good targets for therapeutics designed at arresting, or recovering control of, the cell cycle in aberrantly dividing cells.

The exact role of cdk3 in the cell cycle is not clear. As yet no cognate cyclin partner has been identified, but a dominant negative form of cdk3 delayed cells in G1, thereby suggesting that cdk3 has a role in regulating the G1/S transition.

Although most cdks have been implicated in regulation of the cell cycle there is evidence that certain members of the cdk family are involved in other biochemical processes. This is exemplified by cdk5 which is necessary for correct neuronal development and which has also been implicated in the phosphorylation of several neuronal proteins such as Tau, NUDE-1, synapsin1, DARPP32 and the Munc18/Syntaxin1A complex. Neuronal cdk5 is conventionally activated by binding to the p35/p39 proteins. Cdk5 activity can, however, be deregulated by the binding of p25, a truncated version of p35. Conversion of p35 to p25, and subsequent deregulation of cdk5 activity, can be induced by ischemia, excitotoxicity, and β-amyloid peptide. Consequently p25 has been implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, and is therefore of interest as a target for therapeutics directed against these diseases.

Cdk7 is a nuclear protein that has cdc2 CAK activity and binds to cyclin H. Cdk7 has been identified as component of the TFIIH transcriptional complex which has RNA polymerase II C-terminal domain (CTD) activity. This has been associated with the regulation of HIV-1 transcription via a Tat-mediated biochemical pathway. Cdk8 binds cyclin C and has been implicated in the phosphorylation of the CTD of RNA polymerase II. Similarly the cdk9/cyclin-T1 complex (P-TEFb complex) has been implicated in elongation control of RNA polymerase II. PTEF-b is also required for activation of transcription of the HIV-1 genome by the viral

transactivator Tat through its interaction with cyclin T1. Cdk7, cdk8, cdk9 and the P-TEFb complex are therefore potential targets for anti-viral therapeutics.

At a molecular level mediation of cdk/cyclin complex activity requires a series of stimulatory and inhibitory phosphorylation, or dephosphorylation, events. Cdk phosphorylation is performed by a group of cdk activating kinases (CAKs) and/or kinases such as wee1, Myt1 and Mik1. Dephosphorylation is performed by phosphatases such as cdc25(a & c), pp2a, or KAP.

Cdk/cyclin complex activity may be further regulated by two families of endogenous cellular proteinaceous inhibitors: the Kip/Cip family, or the INK family. The INK proteins specifically bind cdk4 and cdk6. $p16^{ink4}$ (also known as MTS1) is a potential tumour suppressor gene that is mutated, or deleted, in a large number of primary cancers. The Kip/Cip family contains proteins such as $p21^{Cip1,Waf1}$, $p27^{Kip1}$ and $p57^{kip2}$. As discussed previously p21 is induced by p53 and is able to inactivate the cdk2/cyclin(E/A) and cdk4/cyclin(D1/D2/D3) complexes. Atypically low levels of p27 expression have been observed in breast, colon and prostate cancers. Conversely over expression of cyclin E in solid tumours has been shown to correlate with poor patient prognosis. Over expression of cyclin D1 has been associated with oesophageal, breast, squamous, and non-small cell lung carcinomas.

The pivotal roles of cdks, and their associated proteins, in co-ordinating and driving the cell cycle in proliferating cells have been outlined above. Some of the biochemical pathways in which cdks play a key role have also been described. The development of monotherapies for the treatment of proliferative disorders, such as cancers, using therapeutics targeted generically at cdks, or at specific cdks, is therefore potentially highly desirable. Cdk inhibitors could conceivably also be used to treat other conditions such as viral infections, autoimmune diseases and neuro-degenerative diseases, amongst others. Cdk targeted therapeutics may also provide clinical benefits in the treatment of the previously described diseases when

used in combination therapy with either existing, or new, therapeutic agents. Cdk targeted anticancer therapies could potentially have advantages over many current antitumour agents as they would not directly interact with DNA and should therefore reduce the risk of secondary tumour development.

WO 02/34721 from Du Pont discloses a class of indeno [1,2-c]pyrazol-4-ones as inhibitors of cyclin dependent kinases.

WO 01/81348 from Bristol Myers Squibb describes the use of 5-thio-, sulfinyl- and sulfonylpyrazolo[3,4-b]-pyridines as cyclin dependent kinase inhibitors.

WO 00/62778 also from Bristol Myers Squibb discloses a class of protein tyrosine kinase inhibitors.

WO 01/72745A1 from Cyclacel describes 2-substituted 4-heteroaryl-pyrimidines and their preparation, pharmaceutical compositions containing them and their use as inhibitors of cyclin-dependant kinases (cdks) and hence their use in the treatment of proliferative disorders such as cancer, leukaemia, psoriasis and the like.

WO 99/21845 from Agouron describes 4-aminothiazole derivatives for inhibiting cyclin-dependent kinases (cdks), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.

WO 01/53274 from Agouron discloses as CDK kinase inhibitors a class of compounds which can comprise an amide-substituted benzene ring linked to an N-containing heterocyclic group. Although indazole compounds are not mentioned generically, one of the exemplified compounds comprises an indazole 3-carboxylic acid anilide moiety linked via a methylsulfanyl group to a pyrazolopyrimidine.

WO 01/98290 (Pharmacia & Upjohn) discloses a class of 3-aminocarbonyl-2-carboxamido thiophene derivatives as protein kinase inhibitors. The compounds are stated to have multiple protein kinase activity.

US 3,705,175 and DE 2,135,398 (both to Egyt), disclose 6,7-dimethoxyindazole-3-carboxylic acid amides as anti-inflammatory and analgesic agents.

US 3,457,269 (Sterling Drug) discloses indazole-3-carboxylic acid amides, including anilides and pyridylamides, as hypotensive agents.

WO 01/53268 and WO 01/02369 from Agouron disclose compounds that mediate or inhibit cell proliferation through the inhibition of protein kinases such as cyclin dependent kinase or tyrosine kinase. The Agouron compounds have an aryl or heteroaryl ring attached directly or though a CH=CH or CH=N group to the 3-position of an indazole ring.

WO 02/10137 (Signal Pharmaceuticals) discloses a class of indazole derivatives as selective inhibitors of JNK kinase. The indazole derivatives have an aryl, heteroaryl or heterocyclic group linked to the indazole 3-position through an akylene or alkenylene group.

US 6,340,685 (Scios) discloses a class of bicyclic heterocyclic compounds as selective P38 MAP kinase inhibitors. Indazoles are not specifically disclosed.

WO 02/24635 (Fujisawa) discloses a class of amino alcohol derivatives as β-3 adrenergic receptor agonists. The compounds can contain an indazole 3- carboxylic acid anilide group linked to the amino alcohol group.

Summary of the Invention

The invention provides compounds that have cyclin dependent kinase inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the cyclin dependent kinases.

Accordingly, in one aspect, the invention provides a compound of the formula (I) as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

The invention also provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

In a further aspect, the invention provides a method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

This invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I) as defined herein in an amount effective in inhibiting abnormal cell growth.

This invention further provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of the formula (I) as defined herein in an amount effective to inhibit cdk2 activity.

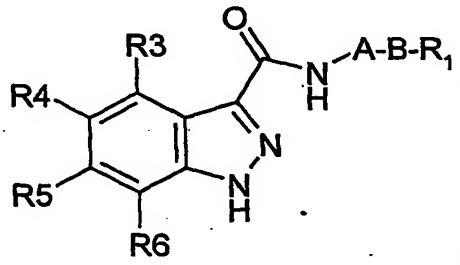
In another aspect, the invention provides a method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

The invention further provides a method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound of the formula (I) as defined herein.

In a further aspect, the invention provides a pharmaceutical composition comprising a novel compound of the formula (I) as hereinbefore defined and a pharmaceutically acceptable carrier.

The invention also provides a novel compound of the formula (I) for use in medicine.

The compounds of the invention are represented by the general formula (I):



(I)

wherein

A is a group R^2 or CH_2-R^2 where R^2 is a carbocyclic or heterocyclic group having from 3 to 12 ring members;

B is a bond or an acyclic linker group having a linking chain length of up to 3 atoms selected from C, N, S and O;

R^1 is hydrogen or a group selected from SO_2R^b, $SO_2NR^7R^8$, $CONR^7R^8$, NR^7R^9 and carbocyclic and heterocyclic groups having from 3 to 7 ring members;

R^3, R^4, R^5 and R^6 are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl

group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

or R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S;

R^7 is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^8 is selected from R^7 and carbocyclic and heterocyclic groups having from 3 to 12 ring members;

R^9 is selected from R^8, COR^8 and SO_2R^8;

or NR^7R^8 or NR^7R^9 may each form a heterocyclic group having from 5 to 12 ring members;

but excluding the compounds N-[(morpholin-4-yl)phenyl-1H-indazole-3-carboxamide and N-[4-(acetylaminosulphonyl)phenyl-1H-indazole-3-carboxamide.

Many of the compounds of the formula (I) are novel. Accordingly, in another aspect, the invention provides a compound of the formula (I) as hereinbefore defined but excluding:

(i) compounds wherein A is phenyl, R^1 is NR^7R^8 and B is a group $-CH(CH_2OH)CH_2-$;

(ii) compounds wherein R^3 and R^6 are both hydrogen and R^4 and R^5 are both methoxy;

(iii) compounds wherein A is unsubstituted pyridyl, B is a bond and R^1 is hydrogen; and

(iv) compounds wherein A is phenyl substituted with one or more of alkyl, alkoxy, alkylsulfanyl, alkylsulfinyl other than *meta*-alkylsulphinyl, alkylsulfonyl other than *meta*-alkylsulphonyl, halogen, nitro and trihalomethyl, B is a bond, and R^1 is hydrogen.

It is preferred that in the compounds of the formula (I), A is other than a thiophene group bearing a 3-aminocarbonyl substituent.

The group A is a group R^2 or CH_2-R^2 where R^2 is a carbocyclic or heterocyclic group having from 3 to 12 ring members. In one particular embodiment, A is a group R^2.

References to "carbocyclic" and "heterocyclic" groups as used herein, either with regard to the group R^2 or any other substituent group, unless the context indicates otherwise include both aromatic and non-aromatic ring systems. Thus, for example, the term "carbocyclic and heterocyclic groups having from 3 to 12 ring members" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated carbocyclic and heterocyclic ring systems.

The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{10} as defined below.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of a pyrazole, imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of heteroaryl groups include but are not limited to pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

In the context of the group R^2, one particular sub-group of compounds of the formula (I) is the group wherein R^2 is pyridyl.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

In the context of the group R^2, preferred aryl groups are groups based on a benzene ring. Thus it may be, for example, a phenyl group which has no substituents other than the group B, or has one or more further substituents R^{10} as defined herein.

Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocylic groups can contain, for example, cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene)), cyclic sulphoxides, cyclic sulphonamides and combinations thereof.

Particular examples include morpholine, piperidine, pyrrolidine, pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dioxan, tetrahydropyran, imidazoline, imidazolidinone, oxazoline, thiazoline, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include tetrahydrofuran, morpholine, piperazine, piperidine, pyrrolidine and pyrrolidone.

The carbocyclic and heterocyclic groups can each be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12

ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10}. In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include carbocyclic or heterocyclic groups. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10}.

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers.

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

The definition "R^a-R^b" as used herein, either with regard to substituents present on the carbocyclic or heterocyclic moiety R^2, or with regard to other substituents present at other locations on the compounds of the formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, C(S) NR^c, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O,

$SC(O)O$, $NR^cC(O)O$, $OC(S)O$, $SC(S)O$, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, $OC(O)S$, $SC(O)S$, $NR^cC(O)S$, $OC(S)S$, $SC(S)S$, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$, $SC(O)NR^c$, $NR^cC(O)\ NR^c$, $OC(S)NR^c$, $SC(S)\ NR^c$, $NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^cNR^c$, S, SO, SO_2, NR^cR^d, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined.

Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

When present, the hydrocarbyl group can be substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituent can be a partially fluorinated or perfluorinated group such as trifluoromethyl.

One or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ wherein X^1 and X^2 are as hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2) and amines (C replaced by NR^c).

In the compounds of the formula (I), B is a bond or an acyclic linker group. The linker group has a linking chain length of up to 3 atoms: in other words the number of atoms in the backbone of the linker group is 1, 2 or 3. Thus, for example, a group $-CH_2-$ has a linking chain length of one, whilst a group $-CH_2-CH_2-$ has a linking chain length of two.

It is preferred that B is a bond or a linker group having a linking chain length of 1 atom.

The atoms making up the backbone of the linker group are selected from C, N, S and O, but preferably the atoms defining the linking chain length are all carbon atoms.

The linker group is typically a straight chain group. By "straight chain" is meant a group that has no branched side chains. In general a straight chain linker group may bear single atom substituents such as halogen and oxo, or substituents each of 1, 2 or 3 atoms, but would not usually have hydrocarbon substituents such as methyl, or larger multi-atom substituents each having four atoms or more such as methoxy or trifluoromethyl for example.

A preferred linker group B is a group $(CH_2)_n$ wherein n is 1, 2 or 3, more preferably 1 or 2, and most preferably 1.

The groups R^3, R^4, R^5 and R^6 are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 7 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members and wherein

one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c;

or R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S.

It is preferred that R^3 is hydrogen or a group selected from halogen, hydroxy, cyano, trifluoromethyl, amino and R^a-R^b.

More preferably R^3 is hydrogen, C_{1-6} alkyl, fluorine or chlorine, and most preferably R^3 is hydrogen.

It is also preferred that R^5 is hydrogen or a group selected from halogen, hydroxy, cyano, trifluoromethyl, amino and R^a-R^b.

More preferably R^5 is hydrogen, C_{1-6} alkyl, fluorine or chlorine, and most preferably R^5 is hydrogen.

In one particular embodiment, R^3 and R^5 are both hydrogen.

It is preferred that R^4 is selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually 5 to 10 ring members), and a group R^a-R^b.

More preferably, R^4 is selected from hydrogen, halogen, a heterocyclic group and a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 5 to 10 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, monocyclic

carbocyclic and heterocyclic groups having from 5 to 10 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$.

Within the above definition of preferred groups R^4, one particular group of compounds is the group in which R^4 is selected from hydrogen, halogen, a heterocyclic group, a group O-Het where Het is a heterocyclic group having from 5 to 10 ring members, C_{1-6} alkyl, C_{1-6} alkoxy, $C(O)NR^cR^b$ and $SO_2NR^cR^b$ wherein R^b is hydrogen or C_{1-6} alkyl.

A further sub-group of compounds of the formula (I) is the group of compounds in which R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S.

Within this sub-group of compounds, preferred compounds are those in which the fused heterocyclic ring has 5 or 6 ring members.

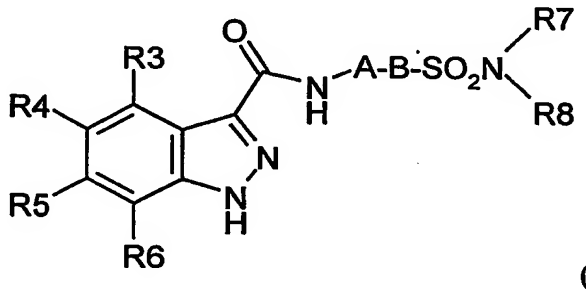
The fused heterocyclic group can be aromatic or non-aromatic and can be optionally substituted by one or more groups R^{10} as hereinbefore defined. In one embodiment, the substituents may be selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and

R^c, R^d, X^1 and X^2 are as hereinbefore defined.

Examples of fused heterocyclic groups include thiazolo, oxazolo, imidazolo and pyrido groups, one particular group being the thiazolo group.

R^6 is preferably selected from hydrogen, methyl, fluorine and chlorine, and more preferably hydrogen and fluorine. Most preferably, R^6 is hydrogen.

One sub-group of novel compounds of the invention is represented by the general formula (II):



(II)

wherein R^3 to R^8, A and B are as hereinbefore defined.

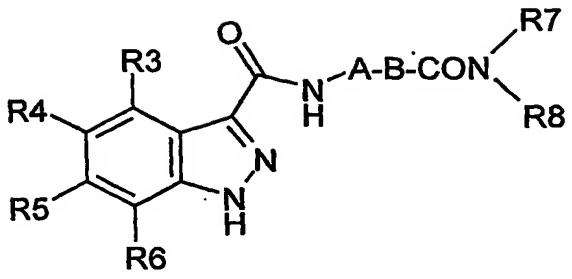
Within the sub-group of compounds of the formula (II), preferred compounds include those wherein A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group.

Another preferred group of compounds within formula (II) is the group of compounds R^7 and R^8 are selected from hydrogen and C_{1-4} alkyl or R^7 and R^8 together with the nitrogen atom form a saturated five or six membered heterocyclic ring having one or two heteroatoms.

Examples of such compounds include compounds wherein R^7 and R^8 together with the nitrogen atom form a saturated heterocyclic ring selected from morpholino, piperidino, piperazino and pyrrolidino.

Further particular examples are compounds in which R^7 is hydrogen and R^8 is hydrogen or methyl.

Another group of novel compounds of the invention is represented by the general formula (III):

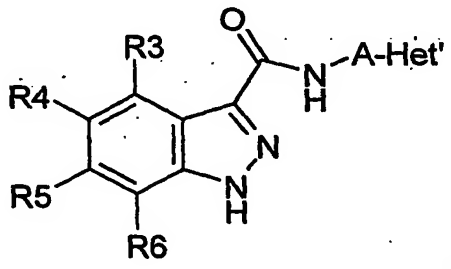


(III)

wherein R^3 to R^8, A and B are as hereinbefore defined.

Within the sub-group of compounds of the formula (III), preferred compounds include those wherein A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group.

A further novel group of compounds of the invention is represented by the general formula (IV):



(IV)

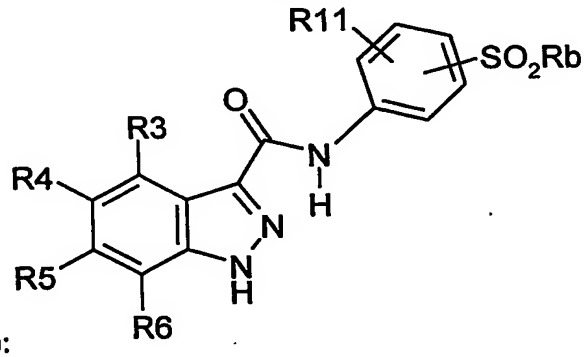
wherein R^3 to R^6 and A are as hereinbefore defined and Het' is a heterocylic group having from 3 to 7 ring members, but excluding the compound N-[(morpholin-4-yl)phenyl]-1H-indazole-3-carboxamide.

Within the sub-group of compounds of the formula (IV), preferred compounds include those wherein A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group.

In one sub-group of compounds of the formula (IV), a carbon atom of the heterocyclic group Het' is linked to the group A.

The group Het' can be, for example, a five membered heteroaryl ring containing 2 or more nitrogen ring members. Examples of such groups include tetrazolyl and imidazolyl.

Another sub-group of novel compounds of the invention is represented by the formula (V):



(V)

wherein R^3 to R^6 and R^b are as hereinbefore defined, and R^{11} represents hydrogen or one or more substituents selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and trifluoromethoxy.

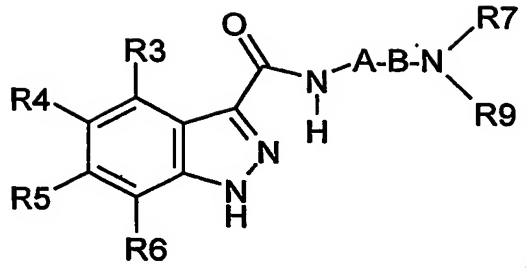
In one sub-group of compounds, the group SO_2R^b is attached to the *meta*-position of the benzene ring.

In another sub-group of compounds, the group SO_2R^b is attached to the *para*-position of the benzene ring.

Typically, but not exclusively, R^{11} is hydrogen.

The group R^b is advantageously a C_{1-4} alkyl group, and in particular a methyl group.

A further sub-group of novel compounds of the invention is represented by the formula (VI):



(VI)

wherein R^3 to R^7, R^9, A and B are as hereinbefore defined.

Within the sub-group of compounds of the formula (VI), typically A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group, preferably a methylene group.

Preferred compounds of the formula (VI) are those wherein R^7 is selected from hydrogen and C_{1-4} alkyl and R^9 is selected from hydrogen, C_{1-4} alkyl and C_{1-4} alkanoyl such as acetyl.

In one general embodiment of the invention, the compounds of the formula (I) may be such that when R^1 is $SO_2NR^7R^8$, neither of R^7 and R^8 is a C_{1-8} hydrocarbyl group in which the carbon atom attached to the nitrogen atom of the group $SO_2NR^7R^8$ is substituted by an oxo group.

In another general embodiment, the compounds of the formula (I) may be such that R^1 is other than the heterocyclic group N-morpholino when B is a bond and A is R^2 wherein R^2 is aryl.

Specific novel compounds of the invention include:
1H-Indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
1H-Indazole-3-carboxylic acid [3-(1H-tetrazol-5-yl)-phenyl]-amide;
1H-Indazole-3-carboxylic acid [4-(acetylamino-methyl)-phenyl]-amide;
1H-Indazole-3-carboxylic acid [4-(2-oxo-pyrrolidin-1-yl)-phenyl]-amide;
1H-Indazole-3-carboxylic acid (3-oxazol-5-yl-phenyl)-amide;
1H-Indazole-3-carboxylic acid [4-(1H-imidazol-4-yl)-phenyl]-amide;
1H-Indazole-3-carboxylic acid (3-methanesulfonyl-phenyl)-amide;

1H-Indazole-3-carboxylic acid [4-(morpholine-4-sulfonyl)-phenyl]-amide;
5-Iodo-1H-indazole-3-carboxylic acid phenylamide;
5-Iodo-1H-indazole-3-carboxylic acid (4-sulfamoyl-phenyl)-amide;
5-Iodo-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
5-Iodo-1H-indazole-3-carboxylic acid (3-methanesulfonyl-phenyl)-amide;
5-Iodo-1H-indazole-3-carboxylic acid [4-(acetylamino-methyl)-phenyl]-amide;
5-Iodo-1H-indazole-3-carboxylic acid (5-nitro-pyridin-2-yl)-amide;
2-amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
5-nitro-1H-indazole-3-carboxylic acid (4-sulfamoyl-phenyl)-amide;
5-nitro-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
5-thiophen-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
5-(3,5-dimethyl-isoxazol-4-yl)-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
5-furan-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;
5-benzofuran-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide; and
5-chloro-1H-indazole-3-carboxylic acid (5-nitro-pyridin-2-yl)-amide.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic,

ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

Compounds of the formula may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

Where the compounds of the formula (I) contain chiral centres, all individual optical forms such as enantiomers, epimers and diastereoisomers, as well as racemic mixtures of the compounds are within the scope of formula (I).

The compounds of the formula (I) are inhibitors of cyclin dependent kinases. As such, they are expected to be useful in providing a means of arresting, or recovering control of, the cell cycle in abnormally dividing cells. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. It is also envisaged that the compounds of the invention will be useful in treating conditions such as viral infections, autoimmune diseases and neurodegenerative diseases for example.

CDKs play a role in the regulation of the cell cycle, apoptosis, transcription, differentiation and CNS function. Therefore, CDK inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or

differentiation such as cancer. In particular RB+ve tumours may be particularly sensitive to CDK inhibitors.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma, ; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

CDKs are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore CDK inhibitors could also be useful in the treatment of the following diseases other than cancer; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and

cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-senstive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

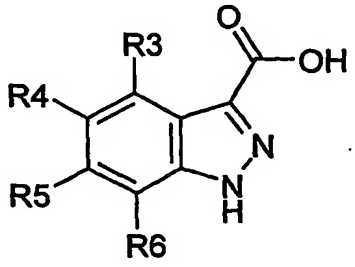
It has also been discovered that some cyclin-dependent kinase inhibitors can be used in combination with other anticancer agents. For example, the cytotoxic activity of cyclin-dependent kinase inhibitor flavopiridol, has been used with other anticancer agents in combination therapy.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

Methods for the Preparation of Compounds of the Formula (I)

Compounds of the formula (I) can be prepared by reacting an amine of the formula H_2N-A-B-R^1 with an indazole 3-carboxylic acid of the formula (X):



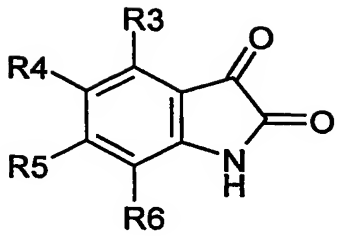
(X)

wherein R^3 to R^6 are as hereinbefore defined. The coupling reaction between the amine and the carboxylic acid (X) can be carried out by forming an activated derivative of the acid such as an acid chloride (e.g. by reaction with thionyl chloride), and then reacting the acid chloride with the amine, for example by the method described in *Zh. Obs. Khim.* 31, 201 (1961), and the method described in US 3,705,175.

Alternatively, and more preferably, the coupling reaction between the carboxylic acid (X) and the amine can be carried out in the presence of an amide coupling reagent of the type commonly used to form peptide linkages. Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan *et al, J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI) (Sheehan *et al, J. Org. Chem., 1961, 26, 2525*), 1-hydroxybenzotriazole (HOBT) (Konig *et al, Chem. Ber.*, 103, 708, 2024-2034), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115, 4397) and phosphonium-based coupling agents such as 1-benzotriazolyloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et al, Tetrahedron Letters*, 1990, 31, 205). A preferred coupling reagent is HATU.

The coupling reaction is typically carried out in a non-aqueous, non-protic solvent such as dichloromethane, dimethylformamide or N-methylpyrrolidine. The reaction can be carried out at room temperature or, where the reactants are less reactive (for example in the case of electron-poor anilines bearing electron withdrawing groups such as sulphonamide groups) at an appropriately elevated temperature. The reaction may be carried out in the presence of a non-interfering base, for example a tertiary amine such as triethylamine or *N,N*-diisopropylethylamine.

Carboxylic acids of the formula (X) can be obtained commercially. Alternatively, compounds of the formula (X) can be prepared from compounds of the formula (XI):



(XI)

by a sequence of reactions involving ring-opening, diazotisation, reduction and cyclisation. Ring opening of the substituted isatin compound to give an *ortho*-aminophenyl-glyoxylic acid derivative can be achieved using an aqueous alkali such as sodium hydroxide with moderate heating, for example to a temperature of 35°C. The amine can then be converted to the diazonium salt by treatment with nitrous acid (for example generated from sodium nitrite and sulphuric acid) at a reduced temperature (e.g. approximately 5°C). The diazonium salt is reduced to form a hydrazine using a reducing agent such as tin (II) chloride and is then cyclised to the indazole by a cyclo-condensation reaction.

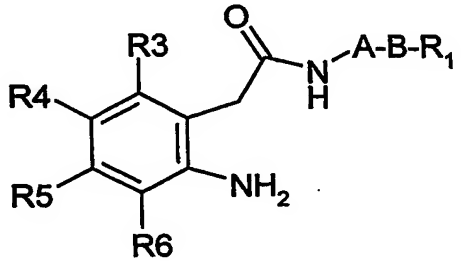
Isatin derivatives of the formula (XI) are available commercially or can be prepared by a variety of known methods.

For example, according to the method described by Hewawasam *et al*, *Tetrahedron Letters*, 1994, 35, 7303-7306, N-protected anilines can be subjected to *ortho*-lithiation and the lithiated intermediate reacted with diethyl oxalate to give an α-ketoester which cyclises to give an isatin upon deprotection of the amino group.

According to the method of Garden *et al*, *Tetrahedron Letters*, 1997, 38, 1501-1504, substituted anilines an be reacted with trichloroacetaldehyde and hydroxylamine in the presence of acid to give an α-isonitrosoacetanilide which cyclises to give an isatin.

According to the method of Kraynack *et al*, *Tetrahedron Letters*, 1998, 39, 7679-7682, substituted isatins can be formed by the γ-dibromination of 2-oxo-indolines and subsequent hydrolysis of the resulting dibromo-compounds.

An alternative route to compounds of the formula (I) involves the reaction of a substituted phenyl acetic acid amide compound of the formula (XII):



(XII)

with nitrous acid or an alkyl nitrite at a reduced temperature (e.g. lower than 20°C and preferably below 0°C) in the presence of a mineral acid such as hydrochloric acid or sulphuric acid or a mixture of hydrochloric acid and acetic acid, for example as described in US 3,705,175.

Compounds of the formula (XII) can be prepared *inter alia* by reduction of the corresponding *ortho*-nitrophenylacetyl compound, for example under conditions analogous to those described in Morie *et al*, *Synth. Commun.*, 1997, 27, 559-566.

Compounds of the formula (I) can also be prepared from other compounds of the formula (I) bearing suitable substituents and suitable reactive groups. For example, compounds wherein one or more of R^3 to R^6 are bromine or iodine, particularly iodine, can be used as intermediates for the preparation of other compounds of the formula (I).

A more detailed description of the processes that can be used to prepare the compounds of the formula (I) can be found in the specific examples set out below.

Pharmaceutical Formulations

The invention also provides compounds of the formula (I) as hereinbefore defined in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular or subcutaneous administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a celluloses or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered

formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.
The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Methods of Treatment

It is envisaged that the compounds of the formula (I) will useful in the prophylaxis or treatment of a range of disease states or conditions mediated by cyclin dependent kinases. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human. The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include cytotoxic agents or agents that arrest cell proliferation, e.g. cisplatin and cyclophosphamide.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using two systems, the details of which are set out below. The two systems were equipped with identical chromatography columns and were set up to run under the same operating conditions. The operating conditions used are also described below.

1. Platform system

System:	Waters 2790/Platform LC
Mass Spec Detector:	Micromass Platform LC
PDA Detector:	Waters 996 PDA

Analytical conditions:

Eluent A:	H_2O (1% Formic Acid)
Eluent B:	CH_3CN (1% Formic Acid)
Gradient:	5-95% eluent B
Flow:	1.5 ml/min
Column:	Synergi 4μm Max-RP C_{12}, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage:	3.5 kV
Cone voltage:	30 V
Source Temperature:	120

2. FractionLynx system

System:	Waters FractionLynx (dual analytical/prep)
Mass Spec Detector:	Waters-Micromass ZQ
PDA Detector:	Waters 2996 PDA

Analytical conditions:

Eluent A:	H_2O (1% Formic Acid)
Eluent B:	CH_3CN (1% Formic Acid)
Gradient:	5-95% eluent B
Flow:	1.5 ml/min
Column:	Synergi 4μm Max-RP C_{12}, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage:	3.5 kV
Cone voltage:	30 V
Source Temperature:	120
Desolvation Temperature:	230

The starting materials for each of the Examples are commercially available unless otherwise specified.

EXAMPLE 1

General Amide Preparative Procedure A

To a solution of indazole-3-carboxylic acid (Fluka) (405 mg, 2.5 mmol, 1.0 equiv) in dichloromethane (10 ml) was added an amine or appropriately substituted aniline

(3.0 mmol, 1.2 equiv), *N,N*-diisopropylethylamine (1.6 ml, 9.0 mmol, 3.6 equiv) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (1.05 g, 2.75 mmol, 1.1 equiv). The mixture was stirred for a period of 24-72 hours and additional *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate was added if necessary. The reaction was quenched with water (10 ml) and dichloromethane (10 ml). The compounds were purified as described in the examples below, and characterised by liquid chromatography and mass spectrometry using either of the systems described above.

EXAMPLE 2

General Amide Preparative Procedure B

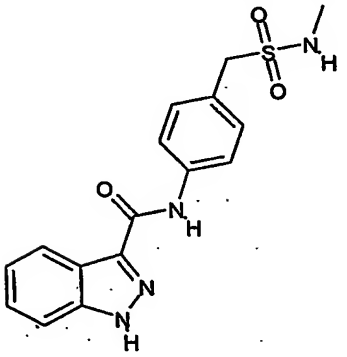
To a suspension of 5-iodoisatin (Lancaster Synthesis) (2.2 g, 8.0 mmol, 1.0 equiv) in water (20 ml) was added NaOH (0.34 g, 8.48 mmol, 1.06 equiv) and the mixture was warmed to approximately 35 °C for 30 minutes to form a solution. The solution was cooled to 5°C and a solution of sodium nitrite (0.62 g, 8.98 mmol, 1.12 equiv) was added dropwise over approximately 30 minutes, keeping the temperature below 10°C. The whole mixture was added dropwise via a cannula to a vigorously stirred solution of concentrated sulphuric acid (1.53 g, 15.6 mmol, 1.95 equiv) in water (20 ml) keeping the temperature below 10 °C. The mixture was stirred for 20 minutes and a solution of tin (II) chloride (3.7 g, 19.52 mmol, 2.44 equiv) in concentrated hydrochloric acid (8 ml) was added dropwise. The mixture was stirred at 5°C for 2 hours and the resulting crude 5-iodoindazole-3-carboxylic acid (a yellow solid) was isolated by filtration and washed several times with water. The yellow solid was then azeotroped with toluene (3 x 100 ml) to remove water prior to the next step. The crude product was dissolved in dichloromethane (36 ml) and split into four 8 ml portions. To the separate solutions of crude 5-iodoindazole-3-carboxylic acid in dichloromethane (8 ml) was added the appropriate amine/aniline (2.4 mmol, 1.2 equiv), *N,N*-diisopropylethylamine (1.2 ml, 7.2 mmol, 3.6 equiv) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.84 g, 2.20 mmol, 1.1 equiv). The

mixture was stirred for a period of 24-72 hours and was then quenched with water (8 ml) and dichloromethane (8 ml). The compounds were purified as described in the examples below, and characterised by liquid chromatography and mass spectrometry using either of the systems described above.

By following either preparative Procedure A or Procedure B, compounds of the formula (I) were prepared as described in Examples 3 to 16.

EXAMPLE 3

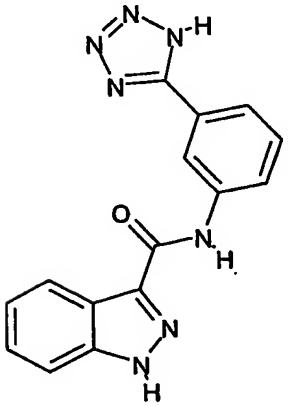
N-[4-(methylsulfonylaminomethyl)phenyl]-1H-Indazole-3-carboxamide



Procedure A was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 119 mg (14%); LCMS 2.92 min, *m/z* $[M+H]^+$ 345.

EXAMPLE 4

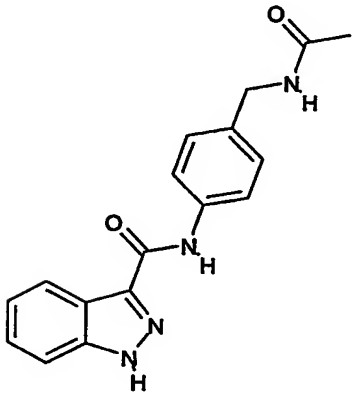
Preparation of N-[3-(1H-tetrazol-5-yl)phenyl]-1H-indazole-3-carboxamide



Procedure A was followed. The water and dichloromethane layers were separated and the aqueous layer was acidified with 2N HCl to form a precipitate. The precipitate was filtered. The title compound was dried *in vacuo* to afford 119 mg (14%); LCMS 2.95 min, *m/z* $[M+H]^+$ 306.

EXAMPLE 5

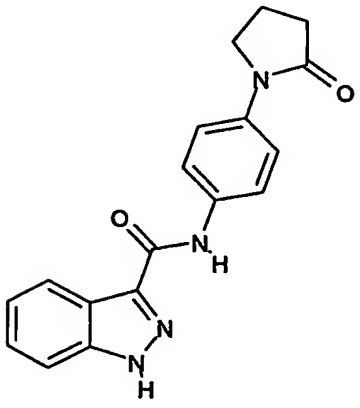
Preparation of N-[4-(acetylaminomethyl)phenyl]-1H-indazole-3-carboxamide



Procedure A was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 190 mg (25%); LCMS 2.68 min, *m/z* $[M+H]^+$ 309.

EXAMPLE 6

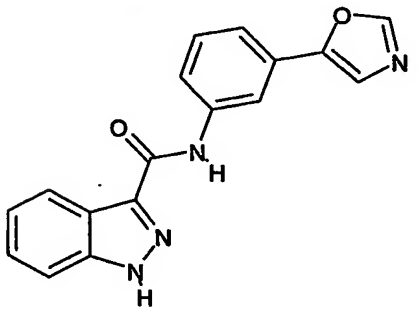
Preparation of acid N-[4-(2-oxopyrrolidin-1-yl)phenyl]-1H-indazole-3-carboxamide



Procedure A was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 311 mg (39%); LCMS 3.00 min, *m/z* $[M+H]^+$ 321.

EXAMPLE 7

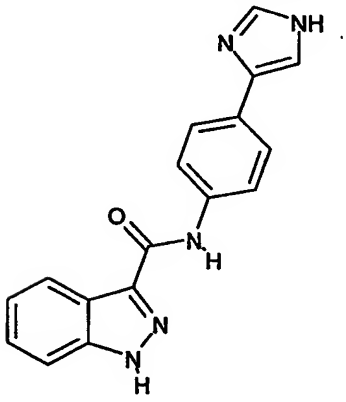
Preparation of N-[3-(oxazol-5-yl)phenyl)-1H-indazole-3-carboxamide



Procedure A was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 276 mg (36%); LCMS 3.42 min, *m/z* $[M+H]^+$ 305.

EXAMPLE 8

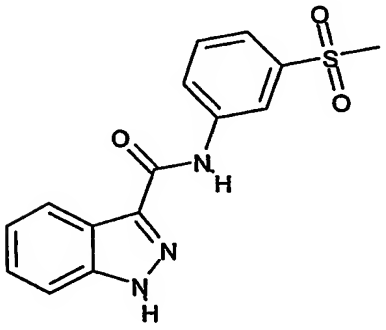
Preparation of N-[4-(1H-imidazol-4-yl)phenyl]-1H-indazole-3-carboxamide



Procedure A was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was further purified by preparative HPLC to afford 1 mg (1%); LCMS 1.99 min, *m/z* $[M+H]^+$ 304.

EXAMPLE 9

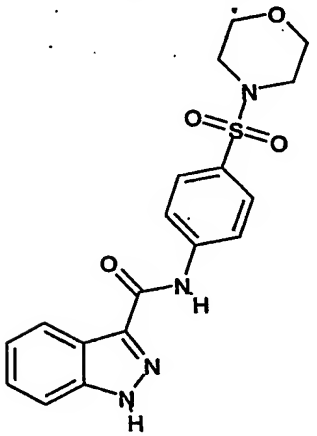
Preparation of N-[3-methanesulfonylphenyl]-1H-indazole-3-carboxamide



Procedure A was followed. The layers were separated and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The title compound was purified by chromatography (SiO_2), eluting with 50% ethyl acetate - petrol, to afford 114 mg (14%); LCMS 3.09 min, *m/z* $[M+H]^+$ 316.

EXAMPLE 10

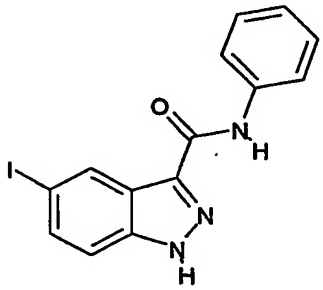
Preparation of N-[4-(morpholine-4-sulfonyl)phenyl]-1H-indazole-3-carboxamide



Procedure A was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was further purified by preparative HPLC to afford 18 mg (2%); LCMS 3.39 min, *m/z* $[M+H]^+$ 387.

EXAMPLE 11

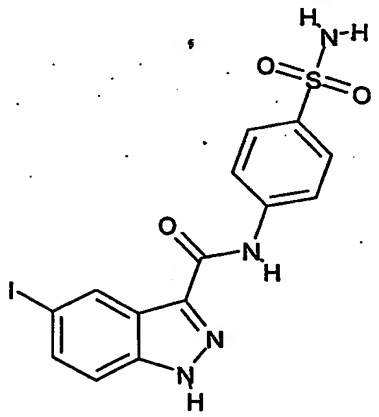
Preparation of N-phenyl-5-iodo-1H-indazole-3-carboxamide



Procedure B was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 53 mg (7%); LCMS 4.11 min, *m/z* $[M+H]^+$ 364.

EXAMPLE 12

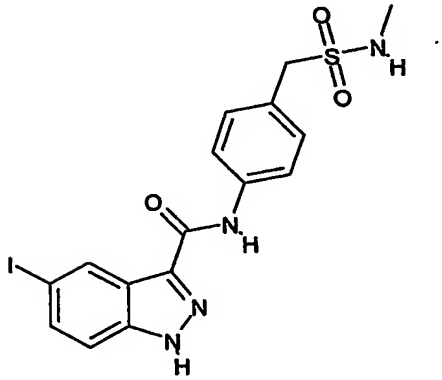
Preparation of N-(4-aminosulfonylphenyl)-5-iodo-1H-indazole-3-carboxamide



Procedure B was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 16 mg (2%); LCMS 3.30 min, *m/z* $[M+H]^+$ 443.

EXAMPLE 13

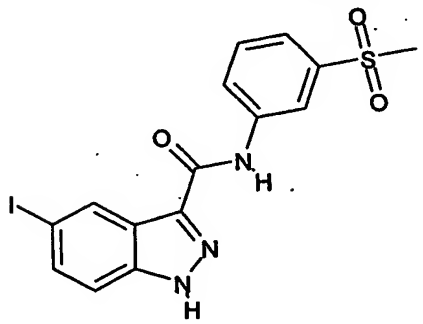
Preparation of N-[4-(methylaminosulfonylmethyl)phenyl)]-5-iodo-1H-indazole-3-carboxamide



Procedure B was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 21 mg (2%); LCMS 3.48 min, *m/z* $[M+H]^+$ 471.

EXAMPLE 14

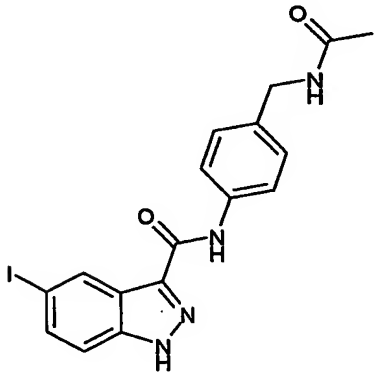
Preparation of N-(3-methanesulfonylphenyl)-5-iodo-1H-indazole-3-carboxamide



Procedure B was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was further purified by preparative HPLC to afford 2 mg (1%); LCMS 4.02 min, *m/z* $[M+H]^+$ 442.

EXAMPLE 15

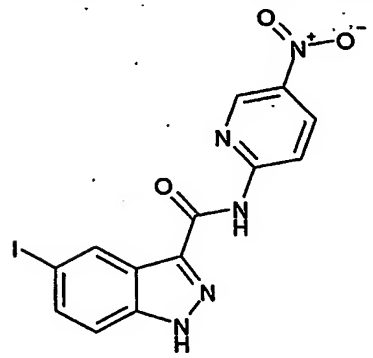
Preparation of N-[4-(acetylaminomethyl)phenyl]-5-iodo-1H-indazole-3-carboxamide



Procedure B was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 16 mg (2%); LCMS 3.44 min, *m/z* $[M+H]^+$ 435.

EXAMPLE 16

Preparation of N-(5-nitro-pyridin-2-yl)-5-Iodo-1H-indazole-3-carboxamide

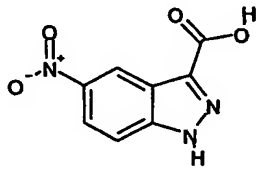


Procedure B was followed. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was dried *in vacuo* to afford 5 mg (1%); LCMS 4.50 min, *m/z* $[M+H]^+$ 410.

EXAMPLE 17

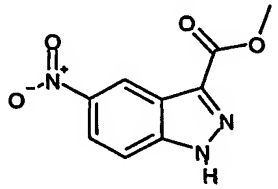
Preparation of 2-Amino-6H-pyrazolo[4',3';3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide

17A. Preparation of 5-Nitro-1H-indazole-3-carboxylic acid



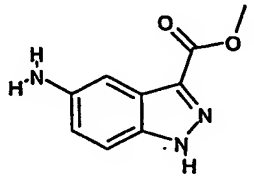
To a suspension of indazole-3-carboxylic acid (Fluka) (5 g, 31mmol) in concentrated H_2SO_4 (30 ml) at 0°C was added KNO_3 (3.13 g, 31 mmol). The reaction was allowed to stir overnight at room temperature, then diluted with water and the products were extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. Evaporation to dryness left the product as a yellow solid as a 7:3 mixture with the 7-nitro isomer; LCMS 2.58 min, *m/z* $[M+H]^+$ 208.

17B. Preparation of 5-Nitro-1H-indazole-3-carboxylic acid methyl ester



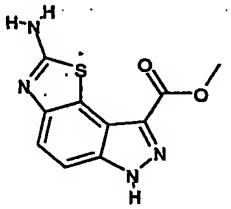
To a suspension of the carboxylic acid of Example 17A (2.5 g, 12.1 mmol) in methanol (40 ml) was added concentrated hydrochloric acid (3 drops). The reaction was heated to reflux over night. The reaction was allowed to cool to room temperature. The solid was filtered and dried in a vacuum oven to leave a yellow solid; LCMS 3.30 min, *m/z* $[M+H]^+$ 222 and *m/z* $[2M+H]^+$ 443.

17C. Preparation of 5-Amino-1H-indazole-3-carboxylic acid methyl ester



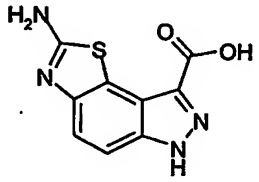
To a suspension of the nitro-indazole of Example 17B (1.23 g, 5.57 mmol) in ethanol (10 ml) was added ethyl acetate (50 ml) and then Pd/C (56 mg) under a nitrogen atmosphere. The atmosphere was exchanged for H_2, and H_2 was bubbled through the reaction mixture for 5 minutes. After three hours the compound was observed to have dissolved completely. The reaction mixture was filtered though Celite and the filtrate evaporated to dryness to leave the product amine [which contains approx. 25% of the 7-nitro isomer].

17D. Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid methyl ester



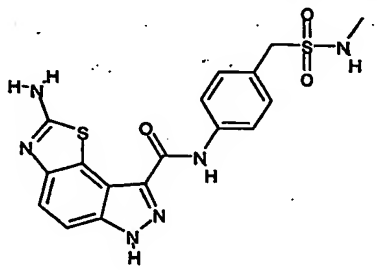
To a solution of the indazole 19B (50 mg, 0.26 mmol) in methanol (1 ml) and -5 °C was added and KSCN (28 mg, 0.29 mmol) and then bromine (7 µl, .13 mmol) slowly. The reaction was left at -5 °C for 2 hours. A brown suspension could be observed to form. The reaction was allowed to warm to room temperature and was filtered. The solid was washed with methanol and dried in a vacuum oven to leave a gray solid; LCMS 1.85 min, *m/z* $[M+H]^+$ 249.

17E. Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid



The methyl ester of Example 17D (790 mg, 3.19 mmol) was suspended in tetrahydrofuran (THF): H_2O (24 ml, 3:1) and $LiOH.H_2O$ (268 mg, 6.37 mmol) was added. The reaction was warmed to 50 °C and left to stir overnight. The solvent was evaporated and ethanol added. The mixture was heated until boiling then filtered. The solid was dried in a vacuum oven to leave the carboxylic acid as a red solid: LCMS 1.53 min, *m/z* $[M+H]^+$ 235.

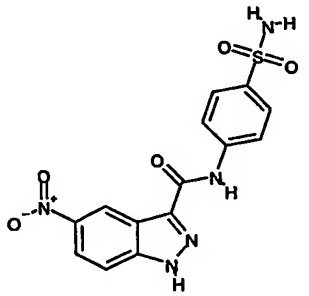
17F. Preparation of 2-Amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



To the carboxylic acid of Example 17E (12 mg, 0.05 mmol) in N-methyl pyrrolidine (NMP) (1.5 ml) was added EDC (16 mg, 0.10 mmol), HOBT (14 mg, 0.10 mmol), NMM (11 µl, 0.10 mmol) and then (4-aminophenyl)-N-methylmethanesulfonamide (15 mg, 0.8 mmol) at room temperature. The reaction was heated to 80°C for 2 hours and then cooled. Ethyl acetate and Na_2CO_3 (aq.) were added (30 ml, 1:1) and the organic layer was separated. The aqueous layer was washed again with ethyl acetate and the combined organic layers were washed with water, then brine and dried over $MgSO_4$. The product was filtered and evaporated to dryness. Purification by preparative HPLC gave the product as a yellow solid: LCMS 2.21 min, *m/z* $[M+H]^+$ 417.

EXAMPLE 18

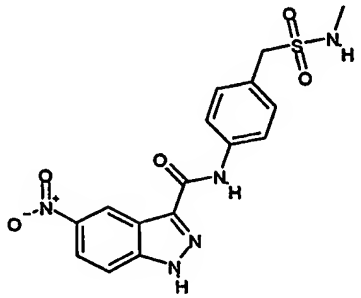
Preparation of 5-Nitro-1H-indazole-3-carboxylic acid (4-sulfamoyl-phenyl)-amide



Procedure B was followed using 5-Nitro-1H-indazole-3-carboxylic acid (Example 17A) and 4-amino-benzenesulfonamide. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was further purified by preparative HPLC as a 8:2 mixture with the 7-nitro isomer; LCMS 2.89 min, *m/z* $[M+H]^+$ 362.

EXAMPLE 19

Preparation of 5-Nitro-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



Procedure B was followed using 5-Nitro-1H-indazole-3-carboxylic acid (Example 17A) and (4-amino-phenyl)-N-methyl-methane sulfonamide. Water and dichloromethane were removed by filtration and the solid was triturated with water and dichloromethane. The title compound was further purified by preparative HPLC: LCMS 3.30 min, *m/z* $[M+H]^+$ 390.

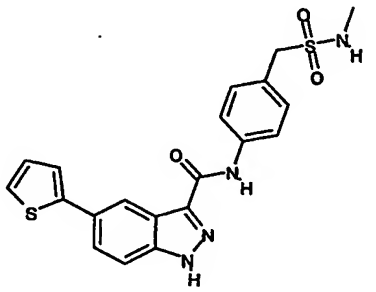
EXAMPLE 20

General Palladium (0) Cross-Coupling Procedure C

To 5-iodo-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide (Example 13) (47 mg, 0.1 mmol, 1.0 equiv.) in toluene (0.8 ml) was added the relevant palladium (0) catalyst (0.02 mmol, 0.2 equiv.). The reaction mixture was degassed by bubbling nitrogen through the mixture and was stirred at room temperature for 5 minutes. The corresponding heteroaryl boronic acid (0.3 mmol, 3.0 equiv) in ethanol (0.8 ml) was added and stirred for 5 minutes. To the mixture was added a solution of potassium carbonate (138 mg, 1.0 mmol, 10 equiv.) in water (2.0 ml) followed by methanol (2.0 ml) and the mixture was sealed in a vial under nitrogen. The mixture was heated between 120°C and 150°C for 15 minutes using a maximum 100-watt power in a microwave. Methanol (5 ml) was added and all solvents were removed under reduced pressure. The compounds were purified as described in the Examples below, and characterised by liquid chromatography and mass spectrometry using either of the systems described above.

EXAMPLE 21

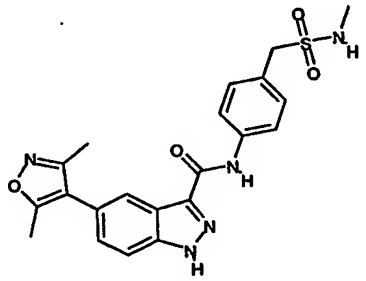
Preparation of 5-Thiophen-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



Procedure C was followed using bis(tri-*t*-butylphosphine)palladium (0) from Strem and thiophene-2-boronic acid (Maybridge). The solid was triturated with water. The title compound was further purified by preparative HPLC to afford 22 mg (52%); LCMS 3.97 min, *m/z* $[M+H]^+$ 427.

EXAMPLE 22

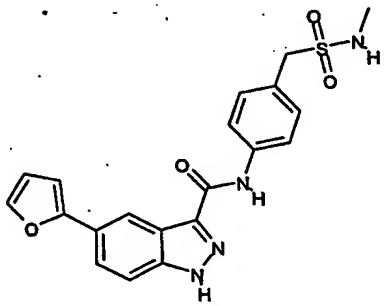
Preparation of 5-(3,5-Dimethyl-isoxazol-4-yl)-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



Procedure C was followed using bis(tri-*t*-butylphosphine)palladium (0) from Strem and 3,5-dimethylisoxazole-4-boronic acid (Maybridge). The solid was triturated with water. The title compound was further purified by preparative HPLC to afford 5 mg (11%); LCMS 3.54 min, *m/z* $[M+H]^+$ 440.

EXAMPLE 23

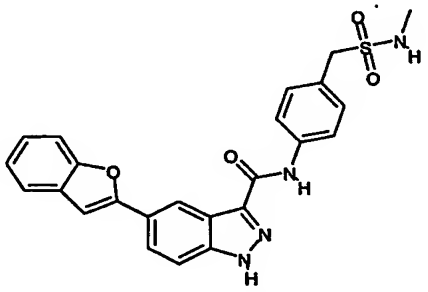
Preparation of 5-Furan-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



Procedure C was followed using bis(tri-*t*-butylphosphine)palladium (0) from Strem and furan-2-boronic acid (Lancaster). The solid was triturated with water. The title compound was further purified by preparative HPLC to afford 15 mg (37%): LCMS 3.82 min, *m/z* $[M+H]^+$ 411.

EXAMPLE 24

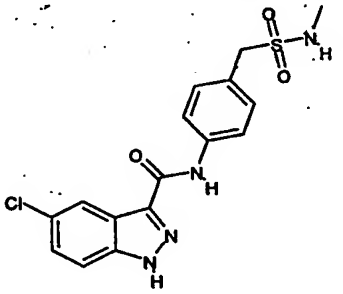
Preparation of 5-Benzofuran-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide



Procedure C was followed using tetrakis(triphenylphosphine)palladium(0) from Aldrich and benzo[b]furan-2-boronic acid (Lancaster). The solid was triturated with water. The title compound was further purified by preparative HPLC to afford 20 mg (36%): LCMS 4.33 min, *m/z* $[M+H]^+$ 461.

EXAMPLE 25

Preparation of 5-Chloro-1H-indazole-3-carboxylic acid (5-nitro-pyridin-2-yl)-amide



To a solution of 5-iodo-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide (Example 13) (42 mg, 0.09 mmol, 1.0 equiv.) in *d*6-dimethyl sulfoxide (0.7 ml) was added copper(I) chloride (401 mg, 4.05 mmol, 45 equiv.). The mixture was heated to 180°C for 15 minutes using a maximum 50-watt power in a microwave. The title compound was purified by preparative HPLC to afford 14 mg (41%); LCMS 3.54 min, *m/z* $[M+H]^+$ 379.

BIOLOGICAL ACTIVITY

EXAMPLE 26

Measurement of CDK2 Kinase Inhibitory Activity (IC_{50})

Compounds of the invention were tested for kinase inhibitory activity using the following protocol.

1.7 µl of active CDK2/CyclinA (Upstate Biotechnology, 10U/µl) is diluted in assay buffer (250µl of 10X strength assay buffer (200mM MOPS pH 7.2, 250mM β-glycerophosphate, 50mM EDTA, 150mM $MgCl_2$), 11.27 µl 10mM ATP, 2.5 µl 1M DTT, 25 µl 100mM sodium orthovanadate, 708.53 µl H_2O), and 10 µl mixed with 10 µl of histone substrate mix (60 µl bovine histone H1 (Upstate Biotechnology, 5 mg/ml), 940 µl H_2O, 35 µCi γ^{33}P-ATP) and added to 96 well plates along with 5 µl of various dilutions of the test compound in DMSO (up to 2.5%). The reaction is allowed to proceed for 5 hours before being stopped with an excess of ortho-phosphoric acid (30 µl at 2%).

γ^{33}P-ATP which remains unincorporated into the histone H1 is separated from phosphorylated histone H1 on a Millipore MAPH filter plate. The wells of the MAPH plate are wetted with 0.5% orthophosphoric acid, and then the results of the reaction are filtered with a Millipore vacuum filtration unit through the wells. Following filtration, the residue is washed twice with 200 µl of 0.5% orthophosphoric acid. Once the filters have dried, 25 µl of Microscint 20 scintillant is added, and then counted on a Packard Topcount for 30 seconds.

The % inhibition of the CDK2 activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the CDK2 activity (IC_{50}).

The results are shown in Table 1 below.

Table 1

Compound of Example No.	CDK2 Activity - IC_{50} Values (μM unless stated)
3	0.732
4	2.000
5	3.084
6	42% @ 30 μM
7	33% @ 3 μM
8	12.662
9	1.176
10	1.144
11	47% @ 1 μM
12	23% @ 3 μM
13	0.110
14	0.939
15	0.256
16	16.100
17F	50%@0.1μM
18	0.20
19	10
21	0.45
22	0.60
23	1.63
24	4.63
25	0.37

PHARMACEUTICAL FORMULATIONS

EXAMPLE 27

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

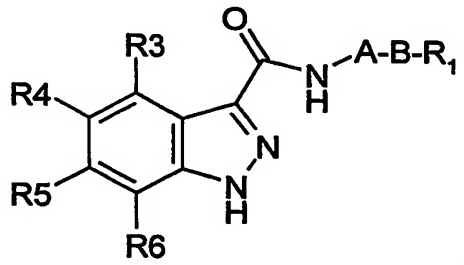
A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the formula (I) for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase:



(I)

wherein

A is a group R^2 or CH_2-R^2 where R^2 is a carbocyclic or heterocyclic group having from 3 to 12 ring members;

B is a bond or an acyclic linker group having a linking chain length of up to 3 atoms selected from C, N, S and O;

R^1 is hydrogen or a group selected from SO_2R^b, $SO_2NR^7R^8$, $CONR^7R^8$, NR^7R^9 and carbocyclic and heterocyclic groups having from 3 to 7 ring members;

R^3, R^4, R^5 and R^6 are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c;

or R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S;

R^7 is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

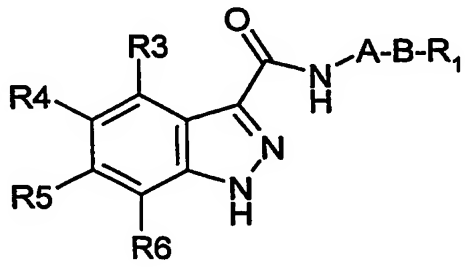
R^8 is selected from R^7 and carbocyclic and heterocyclic groups having from 3 to 12 ring members;

R^9 is selected from R^8, COR^8 and SO_2R^8;

or NR^7R^8 or NR^7R^9 may each form a heterocyclic group having from 5 to 12 ring members;

but excluding the compounds N-[(morpholin-4-yl)phenyl-1H-indazole-3-carboxamide and N-[4-(acetylaminosulphonyl)phenyl-1H-indazole-3-carboxamide.

2. A compound of the formula (I):



(I)

wherein

A is a group R^2 or CH_2-R^2 where R^2 is a carbocyclic or heterocyclic group having from 3 to 12 ring members;

B is a bond or an acyclic linker group having a linking chain length of up to 3 atoms selected from C, N, S and O;

R^1 is hydrogen or a group selected from SO_2R^b, $SO_2NR^7R^8$, $CONR^7R^8$, NR^7R^9 and carbocyclic and heterocyclic groups having from 3 to 7 ring members;

R^3, R^4, R^5 and R^6 are the same or different and are each selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

or R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S;

R^7 is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may

optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^8 is selected from R^7 and carbocyclic and heterocyclic groups having from 3 to 12 ring members;

R^9 is selected from R^8, COR^8 and SO_2R^8;

or NR^7R^8 or NR^7R^9 may each form a heterocyclic group having from 5 to 12 ring members;

but excluding the compounds N-[(morpholin-4-yl)phenyl-1H-indazole-3-carboxamide and N-[4-(acetylaminosulphonyl)phenyl-1H-indazole-3-carboxamide; and further excluding;

(i) compounds wherein A is phenyl, R^1 is NR7R8 and B is a group -$CH(CH_2OH)CH_2$-;

(ii) compounds wherein R^3 and R^6 are both hydrogen and R^4 and R^5 are both methoxy;

(iii) compounds wherein A is unsubstituted pyridyl, B is a bond and R^1 is hydrogen; and

(iv) compounds wherein A is phenyl substituted with one or more of alkyl, alkoxy, alkylsulfanyl, alkylsulfinyl other than *meta*-alkylsulphinyl, alkylsulfonyl other than *meta*-alkylsulphonyl, halogen, nitro and trihalomethyl, B is a bond, and R^1 is hydrogen.

3. A compound according to claim 2 wherein A is other than a thiophene group bearing a 3-aminocarbonyl substituent.

4. A compound according to any one of the preceding claims wherein A is a group R^2.

5. A compound according to any one of the preceding claims wherein B is a bond.

6. A compound according to any one of claims 1 to 4 wherein B is an acyclic linker group having a linking chain length of up to 3 atoms selected from C, N, S and O.

7. A compound according to claim 6 wherein the linker group has a linking chain length of 1 atom.

8. A compound according to claim 6 or claim 7 wherein the atoms defining the linking chain length are all carbon atoms.

9. A compound according to claim 6 or claim 8 wherein the linker group is a straight chain group.

10. A compound according to claim 9 wherein B is a group $(CH_2)_n$ wherein n is 1, 2 or 3.

11. A compound according to claim 10 wherein R^1 is other than hydrogen.

12. A compound according to any one of the preceding claims wherein R^1 is selected from $SO_2NR^7R^8$, $CONR^7R^8$, NR^7R^9 and carbocyclic and heterocyclic groups having from 3 to 7 ring members.

13. A compound according to any one of the preceding claims wherein R^6 is hydrogen.

14. A compound according to any one of the preceding claims wherein R^3 is hydrogen or a group selected from halogen, hydroxy, cyano, trifluoromethyl, amino and R^a-R^b.

15. A compound according to claim 14 wherein R^3 is hydrogen, C_{1-6} alkyl, fluorine or chlorine.

16. A compound according to any one of the preceding claims wherein R^5 is hydrogen or a group selected from halogen, hydroxy, cyano, trifluoromethyl, amino and R^a-R^b.

17. A compound according to claim 16 wherein R^5 is hydrogen, C_{1-6} alkyl, fluorine or chlorine.

18. A compound according to any one of the preceding claims wherein R^3 and R^5 are both hydrogen.

19. A compound according to any one of the preceding claims wherein R^4 is selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a group R^a-R^b.

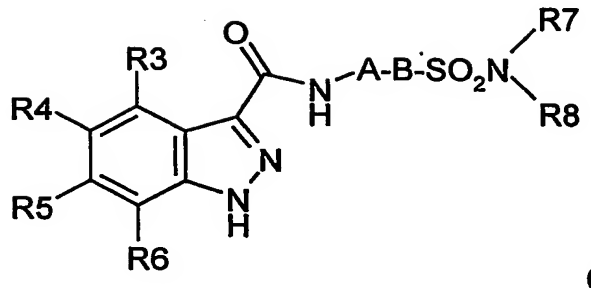
20. A compound according to claim 19 wherein R^4 is selected from hydrogen, halogen, a heterocyclic group and a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 5 to 10 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, monocyclic carbocyclic and heterocyclic groups having from 5 to 10 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$.

21. A compound according to claim 20 wherein R^4 is selected from hydrogen, halogen, a heterocyclic group, a group O-Het where Het is a heterocyclic groups having from 5 to 10 ring members, C_{1-6} alkyl, C_{1-6} alkoxy, $C(O)NR^cR^b$ and $SO_2NR^cR^b$ wherein R^b is hydrogen or C_{1-6} alkyl.

22. A compound according to any one of claims 1 to 13 wherein R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic group having from 5 to 7 ring members and 1, 2 or 3 ring heteroatoms selected from N, O and S.

23. A compound according to claim 22 wherein the fused heterocyclic groups are selected from thiazolo, oxazolo, imidazolo and pyrido groups.

24. A compound of the formula (II):



(II)

wherein R^3 to R^8, A and B are as defined in any one of the preceding claims.

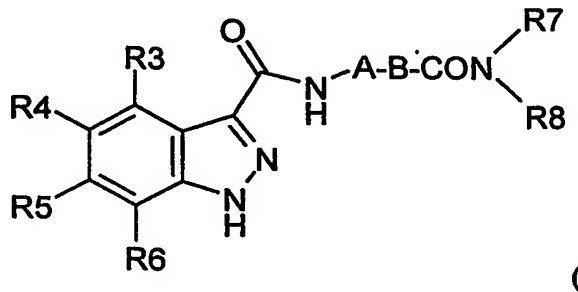
25. A compound according to claim 24 wherein A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group.

26. A compound according to claim 25 wherein R^7 and R^8 are selected from hydrogen and C_{1-4} alkyl or R^7 and R^8 together with the nitrogen atom form a saturated five or six membered heterocyclic ring having one or two heteroatoms.

27. A compound according to claim 26 wherein R^7 and R^8 together with the nitrogen atom form a saturated heterocyclic ring selected from morpholino, piperidino, piperazino and pyrrolidino.

28. A compound according to claim 26 wherein R^7 is hydrogen and R^8 is hydrogen or methyl.

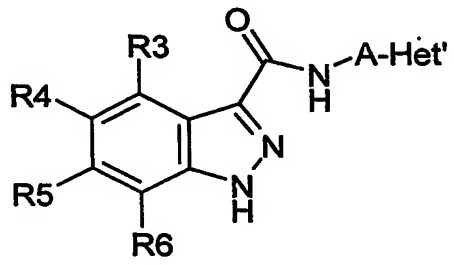
29. A compound of the formula (III):



(III)

wherein R^3 to R^8, A and B are as defined in any one of claims 1 to 23.

30. A compound of the formula (IV):



(IV)

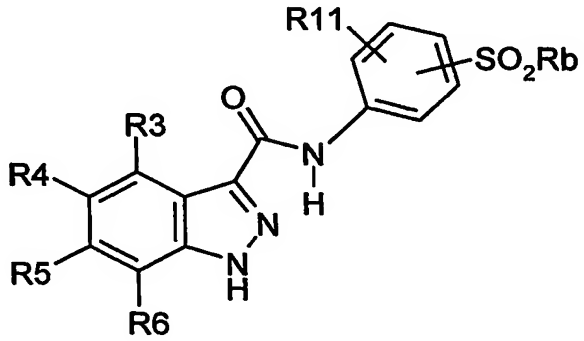
wherein R^3 to R^6 and A are as defined in anyone of claims 1 to 23 and Het' is a heterocylic group having from 3 to 7 ring members, but excluding the compound N-[(morpholin-4-yl)phenyl]-1H-indazole-3-carboxamide.

31. A compound according to claim 30 wherein a carbon atom of the heterocyclic group Het' is linked to the group A.

32. A compound according to claim 31 wherein Het' is a five membered heteroaryl ring containing 2 or more nitrogen ring members.

33. A compound according to claim 32 wherein Het' is selected from tetrazolyl and imidazolyl.

34. A compound of the formula (V):



(V)

wherein R^2 to R^7 and R^b are as defined in any one of claims 1 to 23, and R^{11} represents hydrogen or one or more substituents selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl and trifluoromethoxy.

35. A compound according to claim 34 wherein the group SO_2R^b is attached to the *meta*-position of the benzene ring.

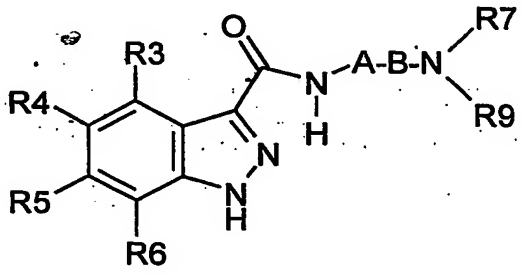
36. A compound according to claim 34 wherein the group SO_2R^b is attached to the *para*-position of the benzene ring.

37. A compound according to any one of claims 34 to 36 wherein R^{11} is hydrogen.

38. A compound according to any one of claims 33 to 35 wherein R^b is C_{1-4} alkyl.

39. A compound according to claim 38 wherein R^b is methyl.

40. A compound of the formula (VI):



(VI)

wherein R^3 to R^7 and R^9 are as defined in any one of claims 1 to 23.

41. A compound according to claim 40 wherein A is a group R^2 wherein R^2 is an aryl group having six ring members and B is a bond or a methylene group.

42. A compound according to claim 41 wherein B is a methylene group.

43. A compound according to claim 42 wherein R^7 is selected from hydrogen and C_{1-4} alkyl and R^9 is selected from hydrogen, C_{1-4} alkyl and C_{1-4} alkanoyl.

44. A compound according to claim 43 wherein R^9 is acetyl.

45. A compound selected from:

1H-Indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

1H-Indazole-3-carboxylic acid [3-(1H-tetrazol-5-yl)-phenyl]-amide;

1H-Indazole-3-carboxylic acid [4-(acetylamino-methyl)-phenyl]-amide;

1H-Indazole-3-carboxylic acid [4-(2-oxo-pyrrolidin-1-yl)-phenyl]-amide;

1H-Indazole-3-carboxylic acid (3-oxazol-5-yl-phenyl)-amide;

1H-Indazole-3-carboxylic acid [4-(1H-imidazol-4-yl)-phenyl]-amide;

1H-Indazole-3-carboxylic acid (3-methanesulfonyl-phenyl)-amide;

1H-Indazole-3-carboxylic acid [4-(morpholine-4-sulfonyl)-phenyl]-amide;

5-Iodo-1H-indazole-3-carboxylic acid phenylamide;

5-Iodo-1H-indazole-3-carboxylic acid (4-sulfamoyl-phenyl)-amide;

5-Iodo-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

5-Iodo-1H-indazole-3-carboxylic acid (3-methanesulfonyl-phenyl)-amide;

5-Iodo-1H-indazole-3-carboxylic acid [4-(acetylamino-methyl)-phenyl]-amide;

5-Iodo-1H-indazole-3-carboxylic acid (5-nitro-pyridin-2-yl)-amide;

2-amino-6H-pyrazolo[4',3':3,4]benzo[1,2-d]thiazole-8-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

5-nitro-1H-indazole-3-carboxylic acid (4-sulfamoyl-phenyl)-amide;

5-nitro-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

5-thiophen-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

5-(3,5-dimethyl-isoxazol-4-yl)-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

5-furan-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide;

5-benzofuran-2-yl-1H-indazole-3-carboxylic acid (4-methylsulfamoylmethyl-phenyl)-amide; and

5-chloro-1H-indazole-3-carboxylic acid (5-nitro-pyridin-2-yl)-amide.

46. A compound according to any one of claims 2 to 45 for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

47. The use of a compound according to any one of claims 1 to 45 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

48. A method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 45.

49. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound as defined in any one of claims 1 to 45 in an amount effective in inhibiting abnormal cell growth.

50. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 45 in an amount effective to inhibit cdk2 activity.

51. A method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 45.

52. A method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound as defined in any one of claims 1 to 45.